B1 30. (New) The method of Claim 29, wherein said mammal is selected from the group consisting of cows, horses, dogs, cats, rats, and humans.

BASIS FOR THE AMENDMENT

Claims 1-11 have been canceled.

Claims 12-30 have been added.

New Claims 12-30 are supported by original Claims 1-11 and the specification as originally filed at page 1, line 21 to page 21, line 22.

No new matter is believed to have been entered by virtue of the present amendment.

REMARKS

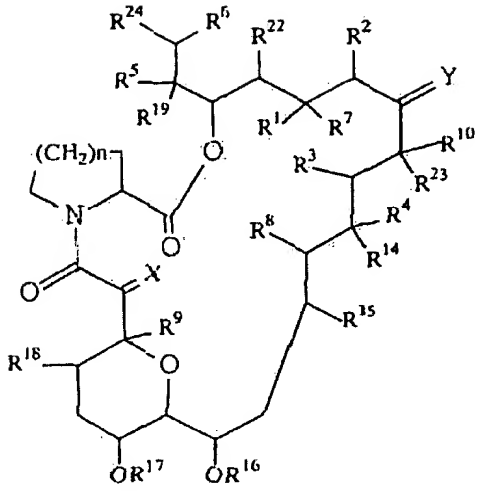
Claims 12-30 are pending in the present application.

Applicants would like to thank Examiner Chism and Examiner Brumback for the helpful and courteous discussion with their undersigned Representative on March 20, 2003. Applicants would also like to thank the Examiner for the indication that the Restriction Requirement (paper number 5) has been withdrawn (paper number 7, page 2, lines 2-6).

The rejection of Claims 1-11 under 35 U.S.C. §112, first paragraph (enablement), is obviated in part by amendment and traversed in part.

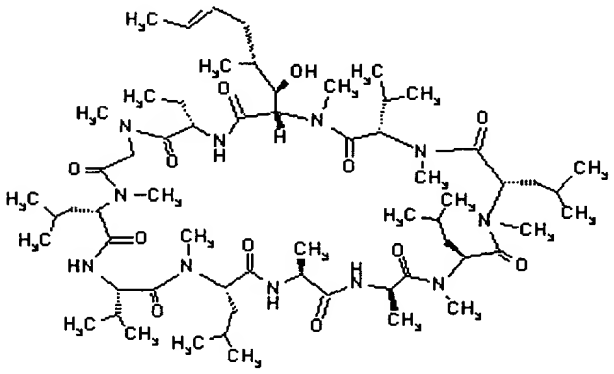
In making this ground of rejection the Examiner states: "the specification, while being enabling for the use of tacrolimus and 33-epi-chloro-33-desoxyascomycin or pharmaceutical compositions thereof for the treatment of MMP-mediated diseases, does not reasonably provide enablement for the use of cyclosporin A or the pharmaceutical compositions thereof for the treatment of MMP-mediated diseases" (paper number 7, page 4, lines 16-20). However, Applicants note that this rejection is based on the enablement of a compound that is outside the scope of the presently claimed invention.

The present invention provides, in part, a method of inhibiting matrix metalloprotease production in a cell in need thereof (Claim 12) or a method of treating a matrix metalloprotease-mediated disease (Claim 19), comprising administering to said cell an effective concentration of one or more macrolides of the formula (I)



(I)

On the other hand, cyclosporin A has the following structure (also see short report attached herewith):



Accordingly, the state of the art and unpredictability of cyclosporin A is of no relevance to the enablement of the claims as currently presented, which are enabled within the context of 35 U.S.C. §112, first paragraph.

Moreover, MPEP §2164.04 states:

> A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

At page 2, line 16 through page 11, line 8, Applicants define the full scope of the macrolides of formula (1), as well as cite relevant references for their synthesis. At page 15, line 1 through page 17, line 11, Applicants provide guidance and definitions for MMP-

production inhibitor, MMP-mediated disease, pharmaceutical compositions, mammals to be treated, and therapeutically effective dosages. Further, at page 17, line 15 through page 20, line 15, Applicants provide a detailed example demonstrating an assay to determine MMP-production inhibition. Moreover, at page 4, line 17 through page 21, line 22, Applicants provide examples of suitable pharmaceutical compositions. Therefore, Applicants have met their burden of clearly defining the scope of the claimed compounds, how to make the compounds, and how to use the compounds. As such, Applicants submit that the present invention is fully enabled.

Withdrawal of this ground of rejection is requested.

The rejection of Claims 1, 3-4, and 7 under 35 U.S.C. §102 over Gottschall is obviated by amendment.

As the Examiner properly indicates, Gottschall discloses the use of the anti-inflammatories indomethacin (INDO) and/or dexamethasone (DEX) for the inhibition of MMP-9 production by beta-amyloid induction (Abstract and page 3079, column 1). Further, as the Examiner has indicated, Claims 1, 3-4, and 7 are intended to be drawn to macrolides of formula (I), but was originally presented in a very broad form so as to encompass INDO and DEX.

Claims 1-11 have now been canceled and replaced with new Claims 12-30, which now recites the inclusion of a macrolide of formula (I) in the independent claims. Accordingly, consistent with the Examiner's recognized deficiencies in the disclosure of Gottschall, the anticipation rejection in view of this reference has been obviated by the amendment presented herein. Specifically, Gottschall fails to disclose or suggest a method of inhibiting matrix metalloprotease production in a cell in need thereof (Claim 12) or a method of treating a matrix metalloprotease-mediated disease (Claim 19), comprising administering to said cell an effective concentration of one or more macrolides of the formula (I).

Withdrawal of this ground of rejection is requested.

The rejection of Claims 5-7 under 35 U.S.C. §112, first paragraph (enablement), is obviated by amendment.

The Examiner rejected Claims 5-7 as lacking enablement for "prevention of MMP-mediated disease." In amendment presented herein, Applicants have removed, without prejudice toward prosecution in an ensuing continuation application, the objected to phrasing.

Therefore, Applicants request withdrawal of this ground of rejection.

The objection of Claims 1-4; the objection of Claim 9 under 37 C.F.R. §1.75(c); the rejection of Claims 1-11 under 35 U.S.C. §112, second paragraph; and the rejection of Claims 1-2 and 5 under 35 U.S.C. §101 are obviated by amendment. Withdrawal of these objections and rejections is requested.

Applicants submit that the present application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

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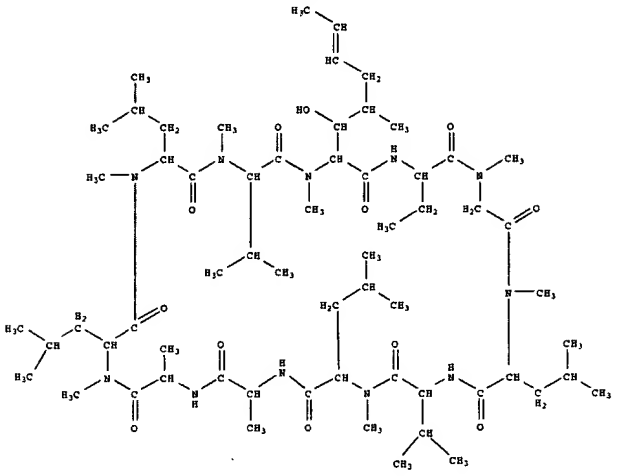
IN THE CLAIMS

Cancel Claims 1-11 and insert therefor new Claims 12-30.

**CYCLOSPORIN A**
**CAS No. 59865-13-3**
First Listed in the *Eighth Report on Carcinogens*



## CARCINOGENICITY

Cyclosporin A is *known to be a human carcinogen* based on studies in humans indicating a causal relationship between exposure to cyclosporin A and human cancer (IARC 1990).

Numerous case reports (IARC 1990) describe cancer (mainly lymphoma or skin cancer) developing in organ transplant recipients, psoriasis patients, and rheumatoid arthritis patients treated with cyclosporin A for immunosuppression. Some of these patients were treated with cyclosporin A alone, whereas others were treated with other immunosuppressive agents in combination with cyclosporin A. The time between treatment initiation and tumor development ranged from 1 month to 10 years. In some cases, tumors regress after discontinuation of treatment with cyclosporin A. Several cohort studies also indicate that cyclosporin A is carcinogenic in humans, inducing a tumor incidence of less than 5% in the patient population (IARC 1990).

In grafted macaques, cyclosporin A increased the incidence of lymphomas, a neoplasm that occurs extremely infrequently in this species of monkey. When given in combination with various other immunosuppressive regimens, cyclosporin A induced a substantial increase in the incidence of lymphomas when compared to immunosuppressive regimens excluding cyclosporin A. In dietary studies, an increased incidence of thymic lymphoma was observed in male mice administered 150 ppm cyclosporin A for 20 to 34 weeks; however, the incidence of tumors in any organ was not increased in male mice administered 1, 4, or 16 ppm cyclosporin A for 78 weeks (IARC 1990). In rats, in a study in which there was no mention of control tumor incidence, renal tumors were detected in more than 50% of streptozotocin-induced diabetic animals administered 10 mg cyclosporin A/kg b.w. orally for 20 weeks (Reddi *et al.* 1991). However, the incidence of tumors of any organ was not increased in rats administered 0.5, 2, or 8 mg cyclosporin A/kg b.w. orally for 95 (males) or 105 (females) weeks (IARC 1990).

## ADDITIONAL INFORMATION RELEVANT TO CARCINOGENESIS OR POSSIBLE MECHANISMS OF CARCINOGENESIS

In initiation-promotion studies, cyclosporin A increased the incidence of lymphoid tumors in male mice either irradiated or treated with *N*-methyl-*N*-nitrosourea (MNU) (IARC 1990), of hepatocellular carcinoma in male rats initiated with diethylnitrosamine (Masuhara *et al.* 1993), and of intestinal adenocarcinoma in male rats administered MNU (IARC 1990). Treatment with cyclosporin A also increased the incidence of cervical lymph node metastasis in Syrian golden hamsters treated with dimethylbenz[*a*]anthracene (Yamada *et al.* 1992) and metastasis of tumors to the liver in male mice inoculated via the portal vein with MCA 38 colon tumor cells (Yokoyama *et al.* 1994) or colon-26 tumor cells (Suzaki *et al.* 1995). In contrast, an increase in adenomas by cyclosporin A was not detected in male mice treated with urethane (IARC 1990), in male rats initiated with 3-methylcholanthrene (Bussiere *et al.* 1991), or in rats treated with *N*-methyl-*N*-nitro-*N*-nitrosoguanidine (IARC 1990).

Cyclosporin A is reported as negative for the induction of genetic damage (gene mutations in prokaryotes, gene mutations and chromosomal aberrations in cultured mammalian cells, chromosomal aberrations and micronuclei in rodent bone marrow cells, DNA repair in mouse testicular cells, and dominant lethal mutations in male mice) (IARC 1990, Zwanenburg and Cordier 1994). However, cyclosporin A was reported to induce a weak increase in sister chromatid exchanges in human lymphocytes *in vitro* and to induce unscheduled DNA synthesis and chromosomal aberrations in the peripheral blood lymphocytes of kidney transplant patients treated with cyclosporin A and prednisolone (IARC 1990).

The most likely explanation for the increased incidence of tumors in patients treated with cyclosporin A is immune suppression (Ryffel 1992).

## PROPERTIES

Cyclosporin A occurs as white prismatic needles from acetone at -15°C. It is slightly soluble in water and saturated hydrocarbons and soluble in methanol, ethanol, acetone, ether, and chloroform (Budavari 1996). Cyclosporin A has a melting point of 148 to 151°C (natural) and 149 to 150°C (synthetic). It is stable in solution at temperatures below 30°C, but is sensitive to light, cold, and oxidization (IARC 1990). Cyclosporin A is incompatible with alkali metals, aluminum, and heat. Hazardous combustion or decomposition products include carbon monoxide, carbon dioxide, nitrogen oxides, hydrogen chloride gas, and phosgene (MSDS 2000).

## USE

Cyclosporin A has been used as an immunosuppressive agent since the mid 1980s. It is used extensively in the prevention and treatment of graft-versus-host reactions in bone marrow transplantation and for the prevention of rejection of kidney, heart, and liver transplants. It has also been tested for the therapy of a large variety of other diseases in which immunological factors may have a pathogenetic role, including Graves' disease, uveitis, Crohn's disease, ulcerative colitis, chronic active hepatitis, primary biliary cirrhosis, diabetes mellitus, myasthenia gravis, sarcoidosis, dermatomyositis, systemic lupus erythematosus, psoriasis, rheumatoid arthritis, and certain nephropathies (IARC 1990, Reents 1996). Cyclosporin A is used alone or in combination with azathioprine, prednisolone, prednisone, antilymphocyte globulin,

actinomycin, cyclophosphamide, methylprednisolone and/or phototherapy (e.g., PUVA, UVB). cyclosporin A is administered orally or intravenously (i.v.). Oral preparations may contain corn, castor, or olive oil in ethanol; i.v. preparations contain 33% alcohol and a castor oil vehicle. In July 1995, a new microemulsion oral formula of cyclosporin A was approved by the FDA (Reents 1996).

## PRODUCTION

Cyclosporin A may be biosynthesized from the fungus *Tolypocladium inflatum* or produced synthetically. It is manufactured commercially in Switzerland (IARC 1990). The 1998 Chemical Buyers Directory identified two American suppliers of the chemical (Tilton 1997). Chem Sources (2001) listed 12 current suppliers. No data on imports or exports of cyclosporin A were available.

## EXPOSURE

The primary routes of potential human exposure to cyclosporin A are intravenous and oral administrations. Patients receiving immunosuppressive therapy for organ transplants, rheumatoid arthritis, and other diseases are exposed to cyclosporin A. Potential occupational exposure may occur for workers formulating or packaging the solutions and for health care professionals administering the drug. A typical oral dose of cyclosporin A is 18 mg/kg daily, beginning 12 hours before transplantation and continuing for one to two weeks. The dosage may subsequently be reduced to 5 to 10 mg/kg or less. Cyclosporin A may also be given by intravenous administration at one-third the oral dose (IARC 1990). This drug is often given for several months to transplant recipients. Cyclosporin A is not included in the National Occupational Exposure Survey (1981-1983) or the National Occupational Hazard Survey (1970) conducted by NIOSH (1990).

## REGULATIONS

FDA regulates cyclosporin A under the Food, Drug, and Cosmetic Act (FD&CA) as a prescription peptide antibiotic drug. Purities and concentrations are given for cyclosporin A oral and injectable dosage forms of drugs. FDA also regulates the use of cyclosporin A in ophthalmic ointment for dogs.

OSHA lists cyclosporin A as a medication that a physician and the employer may wish to review. OSHA also regulates cyclosporin A under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations are summarized in Volume II, Table 53.

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